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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/705,686	11/02/00	CARTER P	P0709P1D3

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EXAMINER	
HELMS, L	
ART UNIT	**PAPER NUMBER**
1642	8

DATE MAILED: 09/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/705,686	Applicant(s) CARTER ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of Group II, claims 10-12 in Paper No. 6 is acknowledged.

2. Claims 1-9 and 13-15 have been canceled.

Information Disclosure Statement

3. The Information Disclosure Statement filed 111/02/00 has been partially considured with regard to all U.S. Patents and the WO 99/60023 document. All other documents were not considured because they were not found in the 08/146,206 application. It is respectively requested that copies of these documents be provided and they will be considured at that time.

Specification

4. The disclosure is objected to because of the following informalities: The instant application claims priority as a DIV to 08/146,206. The instant application should be indicated as a CON of 08/146,206.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 10-12 are indefinite for reciting "the improvement" in claim 10 because the exact meaning of the phrase is not clear. Does the phrase mean improved antigen binding, improvement by being less immunogenic, etc?

b. Claims 10-12 are indefinite for reciting "non-human CDR incorporated into a human antibody" because the exact meaning of the phrase is not clear. Does the phrase mean an entire CDR region or part of the amino acid sequence in a CDR or CDR residues? In addition, can the non-human CDR be incorporated anywhere in the human variable region?

c. Claims 10 and 12 are indefinite for reciting "substituting an amino acid residue for the human residue" in claim 10 because the exact meaning of the phrase is not clear. Does the phrase mean substituting any amino acid residue for the human residue?

d. Claim 12 is indefinite for reciting "no human FR residue other than those set forth in the group has been substituted" because the exact meaning of the phrase is not clear. Does the phrase mean substituting all FR residues in the group or only one or only two, etc?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a humanized antibody wherein the antibody comprises six CDRs from MAb4D5 antibody in a human framework wherein the antibody binds antigen, wherein the antibody comprises FR residues substituted at the recited positions from the Mab4D5 antibody, does not reasonably provide enablement for any humanized antibody with the recited substituted residues or any antibody not having a full set of six CDRs from a non-human antibody or substituting any residues at the recited positions or humanized antibodies which do not bind any antigen . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a humanized antibody comprising any CDRs from any non-human antibody and comprising only one CDR, wherein the antibody

does not bind antigen. The claims are broadly drawn to substituting any amino acid residue at the recited positions, and any improvement as a result of the substitution. The specification teaches a humanized antibody comprising six CDRs from MAb4D5 with substitutions of FR residues and the antibody binds antigen three fold more tightly than the muMAb4D5 did (see page 67-69).

The claims are not comensurate in scope with the enablement provided in the specification. It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that

antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions, have the required binding function. The specification provides no direction or guidance regarding how to produce antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone.

In addition, the specification does not teach substituting just any residue for the human residue at the recited sites. The specification teaches substitution of the non-human residue at the recited positions. One skill in the art would realize that one could not just replace the FR residues recited in claim 10 with just any amino acid and expect to get a functioning antibody.

Therefore, as evidenced by Rudikoff et al and in view of the insufficient guidance and/or working examples concerning the claimed antibodies, one skilled in the art would not know how to use the broadly claimed invention.

Priority

9. The instant application claims priority to 07/715,272. This application is not available for inspection. It is respectively requested that a copy of this application be submitted so that priority can be established. In view that the 07/715,272 application is not available, claims 10-12 in the instant application are granted the priority of 6/15/1992.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 10-12 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 43-105, 115-131 of copending Application No. 08/146,206. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims in the instant application are broader than those in the 08/146,206 application. The claims in the 08/146,206 recite the same scope of a humanized antibody with the same features as claimed in the instant application as well as to an antibody which binds p185HER2. The claims in the instant application are drawn to any antibody.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al (U.S. Patent 5,772,997, priority to 1/25/88, IDS #2) and further in view of Adair et al (WO 91/09667, published 7/11/91, IDS #2).

The claims recite a humanized antibody comprising a non-human CDR incorporated into a human antibody variable domain wherein the improvement comprises substituting non-human amino acid residues recited at specific positions for a human residue.

Hudziak et al teach the 4D5 antibody and chimeric antibodies and human antibodies. Hudziak et al also teach the 4D5 antibody is directed against HER2 and the antibody can be used to treat cancer in humans. Hudziak et al does not teach a humanized antibody comprising FR substitutions at the recited positions. This deficiency is made up for in the teachings of Adair et al.

Adair et al teach a humanized antibodies and a general method for producing humanized antibodies for therapy in humans comprising CDR grafting and substitutions at positions 24 in the heavy chain and 71 in the light chains well as other positions recited in the claims (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Adair et al with CDRs from a non-human and FR substitutions at the recited positions.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Adair et al with CDRs from a non-human and FR substitutions at the recited positions because Hudziak et al teach the antibody binds a cancer antigen and the antibody may be a human or chimeric antibody used for

therapy in humans. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Adair et al with CDRs from a non-human and FR substitutions at the recited positions because Adair et al teach that is desirable to diminish or abolish the undesirable HAMA response for human therapy by humanization and substitutions at specific positions in the FR are required to maintain antigen binding and the antibody comprises only FR substitution at position 37 in the light chain (see page 7, line 6-8). Thus, it would have been obvious to one of skill in the art to produce a humanized antibody with the antibody of Hudziak et al and the method of humanization of Adair et al with FR substitutions as described in Adair et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

14. Claims 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hudziak et al (U.S. Patent 5,772,997, priority to 1/25/88, IDS #2) and further in view of Queen et al (U.S. Patent 5,693,762, priority to at least 2/13/89, IDS #2) and Kabat et al (US Department of Health and Human Services, 1983).

The claims have been described supra.

Hudziak et al has been described supra. Hudziak et al does not teach a humanized antibody comprising FR substitutions at the recited positions. This deficiency is made up for in the teachings of Queen et al and Kabat et al.

Queen et al teach a general method for humanization comprising several criteria for substitution of non-human residues for the human residues in a human FR region (see columns 2-3 and 12-15). Queen et al teach reasons for humanization of antibodies that have therapeutic potential (see column 16, lines 6-27). Queen et al teach computer programs for modeling and all antibodies have similar structures (see column 15, lines 42-56). Queen et al teach specific residues in the FR to substitute (see Table 1).

Kabat et al teach the sequences of all known Ig gamma subtypes.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Queen et al with CDRs from a non-human and FR substitutions at the recited positions.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Queen et al with CDRs from a non-human and FR substitutions at the recited positions because Hudziak et al teach the antibody binds a cancer antigen and the antibody may be a human or chimeric antibody used for therapy in humans. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody of Hudziak et al and produce a humanized antibody as taught by Queen et al with CDRs from a non-human and FR substitutions at the recited positions because Queen et al teach several criteria for substituting non-human residues for the human residues in a humanized antibody method and modeling using consensus framework from many

human antibodies and there are several positions in the FR that interact with CDRs (see column 15, lines 15-35). In addition, Queen et al teach computer programs to construct models of variable regions (see column 43, lines 50 to column 44, line 42) and in view of Kabat et al one skill in the art could determine the amino acids according to Queens method that are numbered according to Kabat et al that would be encompassed by Queen et al's method. Thus, it would have been obvious to one of skill in the art to produce a humanized antibody with the antibody of Hudziak et al and the method of humanization of Queen et al with FR substitutions as described in Queen et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

SHEELA HUFF
PRIMARY EXAMINER